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Original Article

Sympathetic and cardiovascular changes during sleep in narcolepsy with cataplexy patients

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ABSTRACT

Objective: Neural mechanisms underlying sleep-onset rapid eye movement (REM) periods (SOREMPs) in narcolepsy and the role of hypocretin in driving sympathetic changes during sleep are misunderstood. We aimed to characterize autonomic changes during sleep in narcolepsy with cataplexy (NC) patients to clarify the nature of SOREMP events and the effect of hypocretin deficiency on sympathetic activity during sleep.

Methods: We observed 13 hypocretin-deficient NC patients and five healthy controls who underwent nocturnal video-polysomnography (v-PSG) with blood pressure (BP) recording, heart rate (HR), skin sympathetic activity (SSA), and muscle sympathetic nerve activity (MSNA) from the peroneal nerve by microneurography.

Results: Compared to wake, control participants displayed a progressive significant decrease of BP and sympathetic activities during nonrapid eye movement (NREM) sleep and an increase of autonomic activity during REM sleep, as expected. NC patients showed: (1) a decrease of sympathetic activities during SOREMP comparable to NREM sleep stage 1 (N1) but in contrast to the increased activity typical of REM sleep; and (2) physiologic sympathetic change during the following sleep stages with a progressive decrease during NREM sleep stage 2 (N2) and NREM sleep stage 3 (N3) and a clear increase in REM sleep, though BP did not show the physiologic decrease during sleep (nondipper pattern).

Conclusions: SOREMPs in NC patients lack the sympathetic activation occurring during physiologic REM sleep, thus suggesting a dissociated REM sleep condition. In addition, our data indicated that hypocretin plays a limited role in the regulation of sympathetic changes during sleep.

1. Introduction

Narcolepsy with cataplexy (NC) is a chronic sleep disorder characterized by a tetrad of symptoms with largely unknown underlying mechanisms [1]. It has long been claimed that NC symptoms reflect a pathologic activation of brainstem mechanisms inducing a full-blown rapid eye movement (REM) sleep intrusion into active wake, which could be responsible for sleep-onset REM periods (SOREMPs) and other NC symptoms [2,3]. However, the discovery of hypocretin (orexin) neuronal loss in the posterior hypothalamus pinpointed the central role of hypocretin deficiency in NC [4,5], which clashes with the hypothesis of a brainstem dysfunction underlying NC. Accordingly, studies on genetically inherited NC in Dobermans have shown that the mechanism responsible for muscle atonia causing cataplexy is likely located in the hypothalamus and differs from those responsible for REM sleep [6]. Further, autonomic changes during cataplexy differ from those occurring during REM sleep in humans [7].

The SOREMP polysomnographic (PSG) features have been characterized [8,9], but a description of associated autonomic changes is still lacking, thereby precluding a definite conclusion on the nature of SOREMP that may result from a displacement of REM sleep. Further, the role of hypocretin in regulating sympathetic activity during wake has been widely explored [10]; however, it is not clearly documented how it influences sympathetic activity during sleep in humans. Therefore, the aims of our study were to characterize the pattern of sympathetic and cardiovascular changes during SOREMP and the following sleep stages in hypocretin deficient NC patients to help clarify the nature of SOREMPs and the effect of hypocretin deficiency on sympathetic activity during sleep.

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2. Materials and methods

We studied 15 patients with NC confirmed by clinical assessment, by PSG followed by multiple sleep latency test (MSLT), or by low or undetectable cerebrospinal hypocretin-1 levels [11]. Patients were selected for the microneurographic study based on the following criteria: (1) no needle phobia, (2) recordable MSNA in a supine position evaluated by a preliminary wake recording, (3) no major body movements or motor activation during sleep as evaluated by a previous PSG, and (4) drug-naive patients. Microneurographic recording during sleep was successful in 13 NC patients (ages, 34 ± 11 years; five men [Table 1]), whereas two patients were unable to fall asleep. A microneurographic recording was attempted in 15 age-matched healthy controls, but only five controls who were not deprived of sleep (35 ± 21 years; two men) were able to fall asleep and show sleep cycles on the recording. The high dropout rate was likely due to the complex and uncomfortable setting including microneurography and 14 additional parameters. The experimental procedures were approved by the Local Ethics Committee at Bologna University and all participants gave their written informed consent to be enrolled in the study.

2.1. Video-PSG with microneurography

Three to four weeks after a diagnostic PSG, selected participants underwent a second experimental nocturnal video-PSG (v-PSG), including microneurography. During v-PSG recording electrodes were placed according to the international system for the visual scoring of sleep stages, including electroencephalogram (four channels), bilateral electrooculogram, and submentalis and bilateral anterior muscles tibialis electromyogram [12]. Additionally, the following parameters also were recorded during v-PSG: respiratory movements using a thoracic gauge; arterial finger blood pressure (BP), continuously monitored by the volume-clamp method (Finapress BP monitor, Ohmeda 2300, USA) with the cuff around the middle phalanx of the third left finger on the left hand; skin blood flow (Skin Vasomotor Response [SVR]) by an infrared photoelectric transducer (model PPS, Grass Instruments: filter setting 0.5–100 Hz) from the right hand; changes in skin potential (Skin Sympathetic Response [SSR]) by Ag-AgCl surface electrodes (filter setting, 0.1–100 Hz) from the right hand; and multiunit postganglionic muscle sympathetic nerve activity (MSNA) recorded with a tungsten microelectrode with a tip diameter of a few microns inserted into the left peroneal nerve posterior to the fibular head.

A low-impedance reference electrode was inserted subcutaneously a few centimeters away. The nerve signal was amplified (×50,000), filtered (band pass 700–2000 Hz), and fed through a discriminator for further noise reduction and audio monitoring. An MSNA burst represented a mean voltage (integrated) display of the original nerve signal and was obtained by passing the original signal through a resistance–capacitance circuit (time constant, 0.1 s). A recording of MSNA was considered acceptable when it revealed spontaneous pulse-synchronous bursts of neural activity that fulfilled the previously described criteria for MSNA [13].

2.2. Data analysis

2.2.1. Sleep scoring

Sleep stages were visually scored following standard criteria [12] on 30-s epochs. Sleep stages were classified into non-REM (NREM) sleep stage 1 (N1), NREM sleep stage 2 (N2), NREM sleep stage 3 (N3), and REM sleep. Before turning off the lights, 5 min of relaxed wakefulness were recorded from the participants who were invited to stay awake. Afterward, the lights were turned off and participants were allowed to sleep. The following sleep variables were obtained from the overnight study: total sleep time (TST), defined as the total hours of PSG-defined sleep; sleep efficiency (SE, %) was TST divided by lights-off time; sleep latency (SL), defined as the interval between lights off and the first three consecutive epochs of stage N1 sleep or 1 epoch of stages N2, N3 or SOREMP; and the sleep fragmentation index, calculated as the ratio between any sleep stage shift (including awakenings) and the TST per hour [14]. A SOREMP was defined as PSG REM sleep findings (disappearance of muscle tone associated with low-voltage high-frequency electroencephalogram and REMs) occurring within 15 min from sleep onset.

2.2.2. Sympathetic activity

MSNA was expressed as burst incidence (bursts/100 heartbeats). Sympathetic activity going to skin is expressed by the correspondent effector sympathetic responses such as SVR and SSR [15,16]. To simplify data, sympathetic outflow to skin was reported as skin sympathetic activity (SSA) expressing the mean value of both spontaneous SVR and SSR [17]. This choice also was justified,

Table 1
Demographic and clinical data of examined patients and control participants.

Patients	Age (y)	Sex	Dis. dur. (y)	Hypoc. level pg/mL*	MSLT		PSG			
					mSL	SOREMPs (n)	SL	TST (min)	SE (%)	SFI (n/h)
DR	30	F	10	30.8	2′ 0″	3	3′ 30″	44	83	35.5
PA	57	F	16	0	2′ 48″	4	6′	44	82	21
LS	38	M	5	14.3	4′ 42″	2	2′	72.5	79	35
LM	50	F	8	18.4	2′ 36″	5	10′	45	65	63
RA§	24	M	5	0	1′ 42″	4	1′ 30″	141	88	36
MG	26	M	10	0	5′ 4″	3	1′	93	79	17
TS	32	F	6	23.6	0′ 54″	4	4′ 30″	46	53	82
PG	20	F	6	11.2	1′ 0″	5	5′	30	75	24
GV	33	M	18	57.3	13′ 42″	2	6′	77	66	19
ZE	19	F	4	1.3	3′ 30″	5	3′	69	85	24
RM	38	F	23	49.8	7′ 24″	1	7′ 30″	55.5	69	40
AE§	32	F	13	0	2′ 0″	3	6′ 30″	148.5	85	49
FM	45	M	10	17.5	3′ 3″	4	5′	33.5	50	120
Mean	34 ± 11		10 ± 6	14 ± 15	4 ± 1	4 ± 1	4 ± 1	69 ± 38	73 ± 12	44 ± 30
Controls	35 ± 21		–	–	–	–	7 ± 1	69 ± 40	80 ± 17	20 ± 11

Abbreviations: y, years; Dis. dur., disease duration; Hypoc., hypocretin 1; MSLT, mean sleep latency test; PSG, polysomnography; mSL, mean sleep latency; SOREMPs, sleep-onset rapid eye movement periods; SL, sleep latency; TST, total sleep time; min, minutes; SE, sleep efficiency; SFI, sleep fragmentation index; n/h, number per hour F, female; M, male.

* Normal value ⩽110 pg/mL.

§ Patients showing SOREMPs and rapid eye movement sleep phases during the recording.

as the aim of our study was to describe sympathetic tone changes (i.e., skin or muscle) instead of reporting a specific sympathetic response (i.e., SSR or SVR) during the wake-sleep cycle. To be included as a response, SSR amplitude had to exceed 5% of the largest spontaneous skin potential deflection occurring during the baseline wake period, whereas only amplitude greater than 5% of the largest spontaneous SVR occurring during wake was used as an effective skin blood flow change [15]. SSA was expressed as frequency (responses/minute). The analysis of sympathetic activities was made blinded without considering sleep stages, always by the same examiner (V.D.). Subsequently, sleep periods with movements or muscle activation were excluded from the analysis. Furthermore, to prevent sleep instability disrupting the pattern of sympathetic outflow, only periods of stable sleep stages lasting 2 min or longer were selected for the analysis. MSNA time-dependent changes during SOREMP were analyzed considering a mean of a 2-min recording period.

Due to different baseline values among participants, comparisons of sympathetic activities among different recordings also were expressed using relative or normalized metrics. Then in each participant MSNA and SSA changes during sleep also were expressed as the difference from the wake value (=100).

2.2.3. Cardiovascular variables

For each recording period, the computer determined systolic BP (SBP), diastolic BP (DBP), and heart rate (HR) of all individual cardiac cycles. SBP, DBP, and HR individual values were then normalized in the same way as sympathetic activity.

2.3. Statistics

All values are expressed as mean ± standard deviation. Analysis of variance (ANOVA) followed by Bonferroni post hoc testing (Statistica, StatSoft Inc, Tulsa, OK, USA) was used to test MSNA, SSA, SBP, DBP, and HR changes during sleep compared to wake in control participants and NC patients. Repeated-measures ANOVA was used to test within-participants MSNA time-dependent changes during SOREMP and $P < .05$ was considered statistically significant.

3. Results

3.1. Sleep analysis

3.1.1. Control participants

Sleep parameters are reported in Table 1. Sleep began with stage N1 (6 ± 4 min; four participants) followed by N2 (23 ± 18 min; four participants), N3 (30 ± 13 min; three participants), and REM sleep (6 ± 1 min; two participants starting 89 and 70 min after sleep onset).

3.1.2. NC patients

In all participants sleep started with a SOREMP (12 ± 6 min; 13 participants). Subsequently, participants displayed stage N1 (7 ± 6 min; 11 participants), N2 (17 ± 16 min; 11 participants), N3 (26 ± 12 min; seven participants), and REM sleep (9 ± 4 min; two participants starting 142 and 139 min after sleep onset) (Table 1).

3.2. Sympathetic changes

3.2.1. Control participants

A progressive and significant decrease in MSNA and SSA was found during NREM sleep compared to wake (ANOVA [$P < .05$]; Table 2). K-complexes were regularly followed by an MSNA burst during N2 sleep (Fig. 1). During REM sleep (most often during bursts of REMs, thus corresponding to phasic REM sleep), sympathetic activities showed a pronounced increase compared to previous sleep stages; MSNA values were above the wake level (Table 2; Fig. 1), whereas SSA showed a level similar to wakefulness (Table 2).

3.2.2. NC patients

A progressive and significant decrease of SSA was found during SOREMP and NREM sleep (ANOVA [$P < .05$]; Table 2). SOREMP was characterized by a small but nonsignificant MSNA reduction. A further significant MSNA decrease was found during N1, N2, and N3 sleep (Table 2; Fig. 1), mirroring the sympathetic changes in controls. Time-dependent MSNA changes during SOREMP displayed nonsignificant ($P > .5$) progressive decreases (Fig. 2), excluding a delayed sympathetic increase. K-complexes during N2 often were followed by a burst of MSNA (Fig. 1). Similarly SSA showed a progressive decrease during SOREMP, N1, N2, and N3 sleep stages. REM sleep displayed a pronounced sympathetic increase (Table 2; Fig. 1), particularly evident during bursts of REMs.

In two patients we were able to make a direct comparison of sympathetic activities during SOREMP and subsequent REM sleep (Fig. 3). The comparison showed opposite autonomic changes: sympathetic activities decreased during SOREMP with respect to wake but increased during REM with MSNA above the wake level.

3.3. Cardiovascular changes

3.3.1. Control participants

SBP and DBP progressively decreased during NREM sleep, whereas they showed a clear increase in both participants during REM sleep, particularly DBP (Table 2). HR displayed a significant decrease during NREM sleep and a similar wake level during REM sleep (Table 2).

3.3.2. NC patients

No BP and HR significant changes were found during sleep compared to wake (nondipper pattern) (Table 2).

4. Discussion

Our study evaluated sympathetic and cardiovascular changes during SOREMP and physiologic wake-sleep stages in hypocretin-deficient NC patients. The following main results were obtained: (1) compared to wake sympathetic activities decreased during SOREMP in NC patients and during N1 sleep onset in controls, whereas it increased in REM sleep in both groups; and (2) sympathetic activities during NREM sleep stages occurring after SOREMP behaved normally, though BP did not show the physiologic decrease during sleep (nondipper pattern).

4.1. Autonomic changes during SOREMP

Narcolepsy is a chronic sleep disorder characterized by SOREMP showing PSG features analogous to those of physiologic REM sleep [8,18]; however, the underlying autonomic changes have not been previously described. Physiologic REM sleep shows typical sympathetic and cardiovascular changes [19–23] characterized by a pronounced MSNA increase, which usually is above the awake level [20,22], with BP and HR increases showing a similar or higher wake level [20]. The MSNA increase is mainly related to bursts of REMs [20,22]. Similarly sympathetic activity outflow to the skin shows a clear increase during REM compared to NREM sleep [23].

A comparable sympathetic activation was found in our controls during REM sleep. We described the pattern of sympathetic

Table 2
Sympathetic and cardiovascular data during wake-sleep cycle.

	MSNA b/100hb	SSA r/min	SBP mmHg	DBP mmHg	HR b/min	MSNA %	SSA %	SBP %	DBP %	HR %
Controls										
W (n = 5)	38 ± 17	4 ± 1	131 ± 17	66 ± 18	64 ± 8	100	100	100	100	100
N1 sleep (n = 4)	35 ± 13	2 ± 1	125 ± 21	61 ± 21	59 ± 3	**81 ± 9****	**67 ± 16*****	97 ± 6	95 ± 6	**96 ± 2*****
N2 sleep (n = 4)	28 ± 10	**1 ± 0.2****	120 ± 11	64 ± 16	59 ± 6	**87 ± 9***	**26 ± 10*****	**91 ± 6*****	94 ± 8	**92 ± 5*****
N3 sleep (n = 3)	20 ± 5	**1 ± 0.5***	122 ± 8	61 ± 11	60 ± 6	**72 ± 12*****	**31 ± 13*****	**88 ± 12***	**86 ± 10***	**91 ± 7***
REM sleep (n = 2)	42 ± 11	4 ± 2	142 ± 7	85 ± 16	69 ± 13	159 ± 43	84 ± 34	99 ± 5	120 ± 2	91 ± 17
Patients										
W (n = 13)	42 ± 18	3 ± 3	125 ± 15	60 ± 10	62 ± 8	100	100	100	100	100
SOREMP (n = 13)	39 ± 17	**1 ± 0.8***	124 ± 16	59 ± 13	62 ± 5	97 ± 24	**53 ± 6*****	100 ± 7	98 ± 12	100 ± 8
N1 sleep (n = 11)	38 ± 17	**1 ± 0.7***	125 ± 18	60 ± 10	61 ± 6	**86 ± 20***	**36 ± 30*****	99 ± 1	98 ± 11	98 ± 7
N2 sleep (n = 11)	31 ± 15	**1 ± 0.5***	124 ± 17	60 ± 12	60 ± 8	**82 ± 23*****	**52 ± 50*****	101 ± 1	101 ± 12	98 ± 9
N3 sleep (n = 7)	31 ± 15	**0.6 ± 0.5*****	122 ± 13	57 ± 13	62 ± 4	**68 ± 21*****	**36 ± 57*****	98 ± 1	97 ± 12	95 ± 6
REM sleep (n = 2)	50 ± 21	2 ± 2	128 ± 4	61 ± 13	65 ± 8	124 ± 8	53 ± 24	99 ± 2	104 ± 8	97 ± 17

Abbreviations: W, wake; N1, stage 1 nonrapid eye movement (NREM); N2, stage 2 NREM; N3, stage 3 NREM; REM, rapid eye movement; SOREMP, sleep-onset REM period; MSNA, muscle sympathetic nerve activity; SSA, skin sympathetic activity; b/100hb bursts/100 heartbeat; r/min, responses/minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.
Numbers of patients recorded are indicated in brackets.
Due to different baseline values among participants, comparisons among different recordings also were expressed using normalized metrics.
Significant differences from wake are shown in bold: $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$.

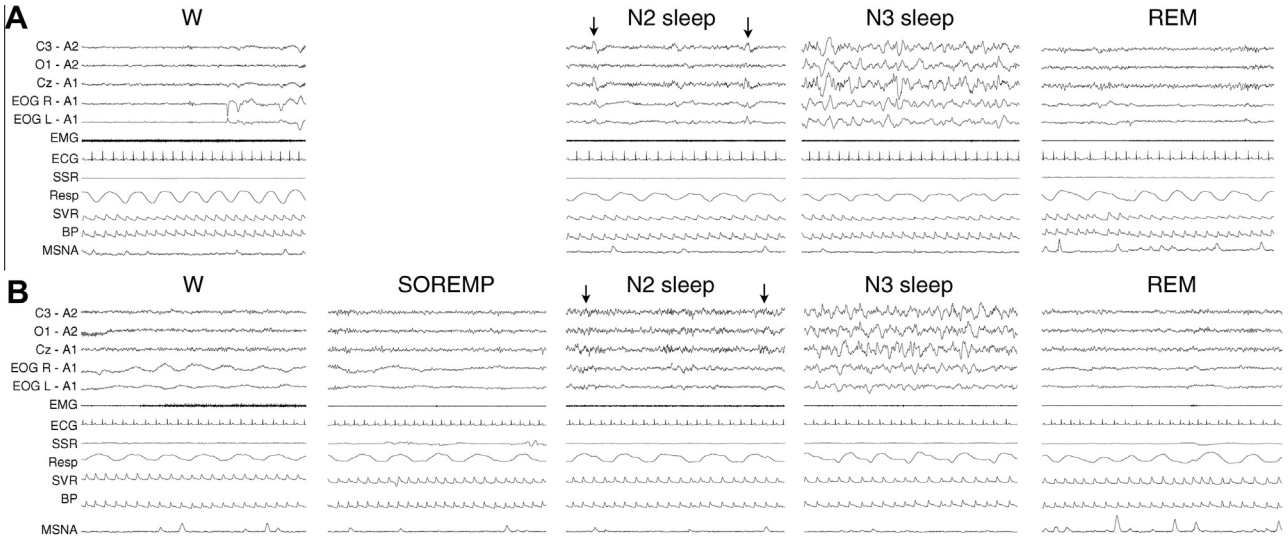

Fig. 1. Video-polysomnography (v-PSG) and microneurographic recording of a wake-sleep cycle and sleep-onset rapid eye movement (REM) period (SOREMP) in a narcolepsy with cataplexy (NC) patient and a healthy control participant. Autonomic changes during the wake-sleep cycle and SOREMP in a healthy control (A) and narcoleptic patient (B). During non-REM (NREM) sleep autonomic activities, including muscle sympathetic nerve activity (MSNA), skin sympathetic activity (SSA), and blood pressure (BP), showed a progressive decrease. MSNA typically was associated with a K-complex during NREM sleep stage 2 (arrow). REM sleep was characterized by a clear BP increase and sympathetic activation with MSNA above the wake level (A). The narcoleptic patient showed a progressive decrease of MSNA and SSA during SOREMP and the following NREM sleep. As a control the K complex often was followed by a MSNA burst. During REM sleep a clear MSNA increase above the wake level and a less evident SSA increase were recorded. BP did not significantly change throughout sleep (B).

activity during SOREMP in hypocretin-deficient NC patients using microneurography. Compared to wake, NC patients displayed a decrease of sympathetic activity (both MSNA and SSA) during SOREMP, which was comparable to that of N1 sleep stage but opposite to the increase occurring during physiologic REM sleep. Accordingly, SOREMP clearly demonstrated a different pattern of sympathetic activation in two patients compared to the following REM sleep episode (Fig. 3).

These data demonstrate that, although SOREMP in NC showed the typical PSG features of REM sleep, it lacked the sympathetic activation characterizing physiologic REM sleep. Accordingly SOREMP could not be considered a complete REM sleep state and the underlying pathogenic mechanism most likely was more complex than a simple displacement of REM sleep periods at sleep onset.

4.2. Autonomic changes during physiologic sleep stages

Sympathetic activity during NREM sleep showed a progressive decrease of both peripheral sympathetic branches (i.e., MSNA, SSA) in NC patients, whereas REM sleep was characterized by the activation of both sympathetic branches with MSNA exceeding the wake value. These changes were comparable to those of our controls and to those described in healthy participants in previous studies [19–23]. Our findings suggest that sympathetic activity during stable sleep stages displays physiologic changes in NC. Therefore, hypocretin has a limited influence on sympathetic changes during sleep which are mainly controlled by the central autonomic network, namely brainstem, limbic, and paralimbic areas [24], as supported by functional imaging [25] and animal studies [26].

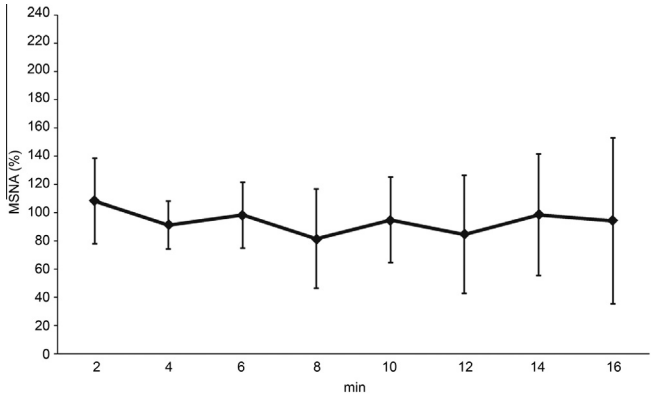

Fig. 2. Time-dependent muscle sympathetic nerve activity (MSNA) changes during sleep-onset rapid eye movement (REM) periods (SOREMPs). Mean time-dependent changes in normalized MSNA during SOREMPs in 13 narcolepsy with cataplexy patients disclosed a progressive but not significant ($P > .5$) decrease of sympathetic activity. This finding demonstrated that the lack of sympathetic activity, typical of REM sleep, was not delayed and did not occur in the last part of the SOREMP. Because of the small number of recorded participants, a similar analysis during REM sleep was not reliable due to the high variability.

In contrast, BP and HR during physiologic sleep did not decrease in patients as expected in healthy participants (nondipper pattern). The same nondipping BP pattern was already reported in hypocretin-deficient narcoleptic mice and in humans [27,28]. The opposite behavior of sympathetic and BP changes during sleep is difficult to explain. A possible explanation could be that sleep fragmentation displayed by NC patients (higher sleep fragmentation index than controls) [29,30] may have particularly affected BP and had a limited influence on sympathetic activity. This hypothesis is supported by evidence that the effect on sympathetic activity usually is short-lived (i.e., seconds) after perturbing events such as a variation of a vigilance state or sleep stage during either wake [31] or sleep [20]. Alternatively the effect on BP is longer due to changes in cardiac output and humoral mechanisms usually requiring minutes [32]. This conclusion also is reinforced by the demonstration that excessive sleep fragmentation with poor sleep quality induced a BP nondipper pattern in participants without hypocretin deficiency [33].

Alternatively the lack of BP decrease during sleep in NC patients may suggest a long-term effect of hypocretin on BP regulation during the wake and sleep cycle, as a similar BP profile during sleep without an associated increase in sleep fragmentation was described in hypocretin-deficient narcoleptic mice [27].

4.3. Pathogenic mechanisms underlying NC

NC has traditionally been considered a disorder of REM sleep [2,3]. More recently, the proposed pathogenic mechanism underlying NC has been questioned, as a canine model of the disease demonstrated an intact ultradian rhythm of REM sleep occurrence and the sites responsible for muscle atonia characterizing cataplectic attacks differed from those responsible for REM sleep [6]. Furthermore, the association between narcolepsy and hypocretin abnormalities [1,4,5,34] and the description of symptomatic cases of NC associated with hypothalamic lesions [35] have focused on hypocretin signaling and on the posterior hypothalamus as the main pathogenic mechanism and the site responsible for NC.

In agreement with this hypothesis, we found that SOREMP represents a dissociated manifestation of REM sleep lacking the typical sympathetic activation occurring during physiologic REM sleep in both controls and NC patients. This finding supports the possibility that SOREMP arises from the release of inhibitory control by a higher center (i.e., hypothalamus) on brainstem mechanisms generating REM sleep. Independent pathways mediating REM sleep phenomena have been described in animals [36], thus providing a basis for their occasional dissociation in pathologic states [37,38]. The possibility that sympathetic activation during SOREMP was delayed and not synchronized with electroencephalogram was unlikely, as time-dependent MSNA change analysis showed a progressive decrease of activity during this sleep phase (Fig. 2).

Furthermore, these data are in line with the concept of status dissociatus underlying several sleep disorders, including disorders of arousal, REM sleep behavior disorder, among others [39,40],

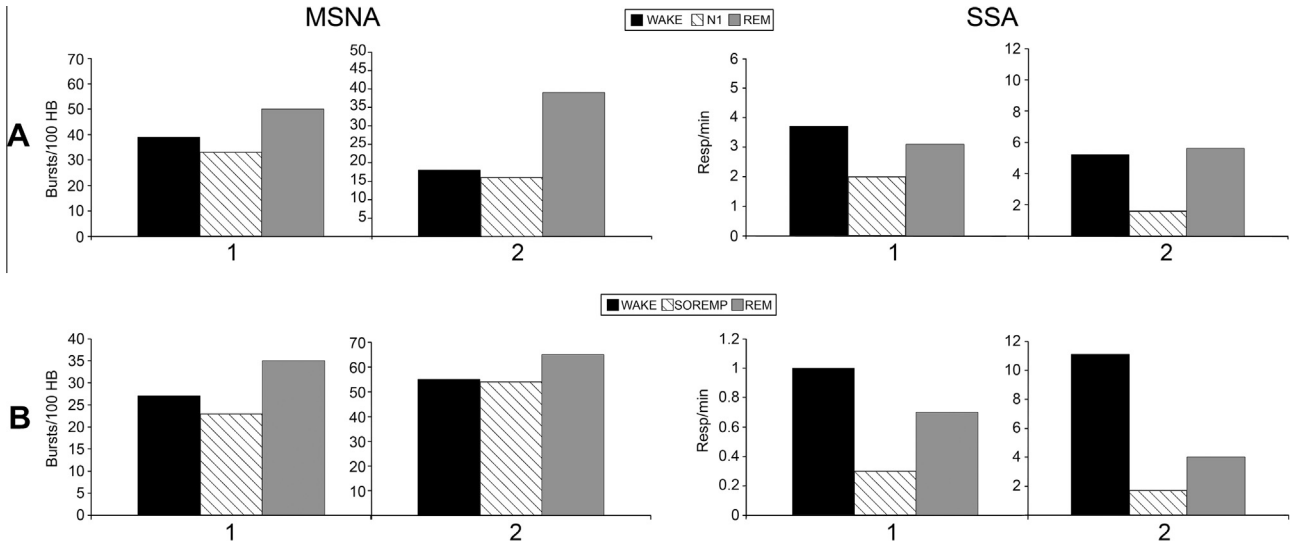

Fig. 3. A direct comparison of autonomic changes during sleep-onset phases and rapid eye movement (REM) sleep. Only two controls (A) and two narcolepsy with cataplexy (NC) patients (B) showed REM sleep allowing a direct comparison of autonomic changes during sleep-onset phases (nonrapid eye movement sleep stage 1 [N1] in controls and sleep-onset REM periods [SOREMs] in NC patients) and REM sleep. Both controls (identified by a number in the *x*-axis) showed a slight decrease of sympathetic activities during sleep onset (N1) compared to wake with a subsequent clear increase during REM sleep when the muscle sympathetic nerve activity (MSNA) value was above the wake level (A). Similarly SOREMPs were characterized by a slight MSNA and skin sympathetic activity (SSA) decrease in both NC patients (number in the *x*-axis), whereas REM sleep showed a pronounced MSNA increase (above the was value) and a less evident SSA increase. These findings supported the conclusion that the pattern of sympathetic activation occurring during SOREMP was comparable to N1 but different from REM sleep (B).

expressing a lack of coordination in sensory, motor, autonomic, and cerebral processes coupled with sleep.

Another important contribution of our study was that sympathetic activities during stable sleep stages showed a physiologic change in participants with hypocretin-deficient NC. This finding argues against a major role of hypocretin in influencing sympathetic activities during sleep; however, data on REM sleep are limited and require further studies. Hypocretin neurons most likely are relevant in orchestrating the neural circuits controlling autonomic functions and emotional behaviors during wake and arousal, such as those involved in the defense response [10]. Accordingly, hypocretin neurons are specifically active during wake but silent or occasionally active during sleep in animals [41].

4.4. Limitations

The main limitation of our study is the low number of controls and physiologic REM sleep stages recorded. Nevertheless the difficulty of recording sympathetic activity by microneurography during sleep, particularly during REM sleep, in humans was confirmed by the few data published on the topic [19–23]. To our knowledge, only 22 REM sleep phases recorded by microneurography have been reported to date, and the number of physiologic REM sleep episodes described in the same paper (range, 4–6) was the same as in our study ($n = 4$). Additionally, our complex setting protocol, which allowed us to record both peripheral sympathetic branches, was objectively uncomfortable mainly for healthy participants who had a normal sleep propensity and were not sleep deprived to avoid any artificial influence on sleep and autonomic regulation. In contrast, untreated NC patients had a tendency to fall asleep, thereby explaining the low-recording dropout rate compared to controls. However, physiologic autonomic changes during sleep (including REM sleep) reported in previous studies were qualitatively similar to those displayed by our controls, which support our main conclusions.

In addition, we cannot exclude that the differences in sympathetic activity between SOREMP and REM sleep phases could be independent of NC mechanisms and regulated by the circadian clock; however, this possibility seems unlikely due to the short delay (2 h) separating these two sleep phases. Further, no SOREMP episodes were recorded in controls and we were unable to establish the specificity of autonomic SOREMP data in NC. More data including SOREMP in other sleep disorders such as sleep deprivation are needed to clarify these aspects and to establish the specificity of the autonomic changes during SOREMP in NC.

5. Conclusions

Our data suggest that SOREMP in NC lacks the typical sympathetic activation occurring during physiologic REM sleep and may represent a dissociated REM sleep state. In addition, our data indicated a limited role of hypocretin in driving sympathetic changes during sleep.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.12.005.

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